TRANSFUSION MEDICINE UPDATE

The Institute For Transfusion Medicine

August, 1995

THE FACTOR V LEIDEN MUTATION

A MAJOR RISK FACTOR FOR INHERITED THROMBOSIS

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Introduction Traditional attempts to identify an underlying cause of familial thrombosis by testing for antithrombin III, protein C, and protein S have only rarely provided an explanation for a patient's thrombotic event. Recently, studies have clearly shown that a mutation of clotting factor V is highly associated with thrombosis and may account for as much as 25% of all cases of venous thrombosis of unknown cause. In addition, knowledge that a patient carries this gene may have significant clinical implications.

Pathophysiology The factor V mutation, named factor V Leiden after the site of its discovery, is due to a point mutation in the normal factor V molecule. This mutation renders the factor V molecule less susceptible to the action of activated protein C, a natural anticoagulant. This in turn appears to shift the patient's overall hemostatic balance toward thrombosis, especially venous thrombosis.

Incidence The incidence of the factor V Leiden mutation in both European and American populations has been repeatedly found to be surprisingly high. The best evidence from the United States indicates that 6% of the population carries the gene for the factor V mutation. The reason for its persistence at such a high level is unclear.

Thrombotic Risk Recent studies indicate that a person heterozygous for the factor V Leiden mutation has a risk of thrombosis seven times that of the general population. The homozygous state confers a 79 fold increased risk compared to a control population. Of particular importance is a study from the United Kingdom indicating that women with the mutation who take oral contraceptives have a risk of thrombosis which is 35 times greater than the general population. This has prompted a concern that women who are considering the use of oral contraceptives might need to be screened for the mutation beforehand.

Diagnosis Initially, a screening test for the mutation called the activated protein C (APC) resistance test was described. This modification of the activated partial thromboplastin time (APTT) basically evaluates the ability of a thrombotic patient to mount an anticoagulant response to activated protein C. If the APC resistance screening test is positive, confirmatory testing for the factor V Leiden mutation by a polymerase chain reaction (PCR) test is recommended.

Testing Limitations Published reports and our experience indicate that positive APC resistance test results may be seen in patients with systemic lupus, lupus anticoagulants, protein S deficiency, patients who are taking estrogens or oral contraceptives, and those who are pregnant, without having the factor V mutation present. In addition, heparinized patients cannot be tested for APC resistance. Patients taking oral anticoagulants (Coumadin) may be tested for APC resistance using a modified procedure, but the laboratory needs to be notified in advance or the results may be compromised. In contrast, the PCR test for the mutation is done on white blood cells and is not affected by any of the aforementioned clinical situations and provides a definitive answer albeit at a slightly higher cost. Therefore, we sometimes recommend testing directly for the mutation in clinical situations where the APC resistance test is not practical.

Therapy Adult patients diagnosed with the factor V mutation who have had a venous thrombosis are currently advised to take lifelong Coumadin. In addition, post-operative prophylaxis should be mandatory for any surgical procedures. Women who have the mutation should not take oral contraceptives, and should be counselled with regard to the increased risk of thrombosis during pregnancy. Lastly, testing of family members should be undertaken when a relative is found to have the mutation.

Summary The newly described factor V Leiden mutation represents a major advance in the ability to diagnose and counsel patients with thrombosis. It is extremely common, affecting 6% of the U.S. population and may account for a large proportion of patients with previously unrecognized causes of thrombosis.■

For further information regarding the factor V mutation contact Dr. Bontempo at 412-622-7310 or Dr. Cortese-Hassett at 412-622-7336.

References

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Ridker PM, Hennekens CH, Lindpainter K, Stampfer MJ, Eisenberg PR, Miletich JP: Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. N Eng J Med 332:912-7, 1995.

The Institute for Transfusion Medicine and the University of Pittsburgh's Department of Continuing Education are sponsoring a one-day postgraduate course devoted to advances in transfusion medicine on Saturday, September 23, 1995, at the Sheraton Hotel, Station Square in Pittsburgh. If you are interested in receiving a brochure, please call Patricia Simko, (412) 647-9541.

Erratum:

The erythropoietin reference range as published in the July Transfusion Medicine Update was reported in error and should have been reported as 15-59 min/ml instead of 15-19 min/ml.